Chromatin regulation by Brg1 underlies heart muscle development and disease.

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Public Summary:
This article describes how different classes of epigenetic regulators (BAF, HDAC, PARP) work together to control heart muscle development in embryos and heart function in the adult.

Scientific Abstract:
Cardiac hypertrophy and failure are characterized by transcriptional reprogramming of gene expression. Adult cardiomyocytes in mice primarily express alpha-myosin heavy chain (alpha-MHC, also known as Myh6), whereas embryonic cardiomyocytes express beta-MHC (also known as Myh7). Cardiac stress triggers adult hearts to undergo hypertrophy and a shift from alpha-MHC to fetal beta-MHC expression. Here we show that Brg1, a chromatin-remodelling protein, has a critical role in regulating cardiac growth, differentiation and gene expression. In embryos, Brg1 promotes myocyte proliferation by maintaining Bmp10 and suppressing p57(kip2) expression. It preserves fetal cardiac differentiation by interacting with histone deacetylase (HDAC) and poly (ADP ribose) polymerase (PARP) to repress alpha-MHC and activate beta-MHC. In adults, Brg1 (also known as Smarca4) is turned off in cardiomyocytes. It is reactivated by cardiac stresses and forms a complex with its embryonic partners, HDAC and PARP, to induce a pathological alpha-MHC to beta-MHC shift. Preventing Brg1 re-expression decreases hypertrophy and reverses this MHC switch. BRG1 is activated in certain patients with hypertrophic cardiomyopathy, its level correlating with disease severity and MHC changes. Our studies show that Brg1 maintains cardiomyocytes in an embryonic state, and demonstrate an epigenetic mechanism by which three classes of chromatin-modifying factors-Brg1, HDAC and PARP-cooperate to control developmental and pathological gene expression.